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PROTECTIVE THERAPIES FOR MONOMETHYLHYDRAZINE: COMPARISON OF PYRIDOXINE AND PHYSICAL RESTRAINT IN THE MONKEY

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

A. A. Thomas

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This study compared convulsive and related pre-convulsive responses to monomethylhydrazine (MMH) in three groups of chaired rhesus monkeys. One group served as a control and the other two as experimental groups to evaluate the influence on these measures of arm restraint and pyridoxine, respectively. Control animals displayed emesis, pre-ictal responses and generalized seizures within the first 75 min post-MMH-injection. Pyridoxine treated animals showed emesis but no pre-ictal or ictal behavior during this

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period, while arm restrained animals showed no emesis, pre-ictal or ictal behavior. Control animals exhibited a criterion of three generalized seizures, after which chemotherapy was administered within the first 100 min post-MMH-injection. Neither pyridoxine treated nor arm restraint animals showed any generalized seizures during a standard 240 min observation period, although both groups eventually displayed emesis and pre-ictal responses. The protective effects of pyridoxine were interpreted within the context of established neurochemical influences of the hydrazines on synthesis of the inhibitory neurotransmitter, gamma amino-butyric acid. The protective effect of restraint was related to similar observations in the literature and discussed in terms of CNS activation, inhibitory neurotransmitter dynamics, and correlated somatosensory EEG patterns indicative of an anticonvulsant "immobilization state."

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 2312, Task 2312V1, Work Unit 2312V113. Experiments were performed on Contract AF F33615-76-C-5014, by the School of Medicine, University of California, Los Angeles, California, 90024.

The experiments were conducted by M. B. Sterman, Ph.D., of the Veterans Administration Medical Center, Sepulveda, California 91343, S. J. Goodman, M.D. of Harbor General Hospital, Torrance, California 90509, and M. D. Fairchild, Ph.D., of the Veterans Administration Hospital, Long Beach, California 90804. Kenneth C. Back, Ph.D., was contract monitor for the Aerospace Medical Research Laboratory.

PROTECTIVE THERAPIES FOR MONOMETHYLHYDRAZINE: COMPARISON OF PYRIDOXINE AND PHYSICAL RESTRAINT IN THE MONKEY

INTRODUCTION

Early studies of the effects of neuromuscular blocking agents on hydrazine-induced convulsions established the central mediation of these seizures (Witkin and Weatherby, 1955) but failed to recognize the alteration of convulsive response resulting from paralysis. Later experiments carried out within our research program showed that neuromuscular paralysis significantly delayed the onset of seizures from exposure to both unsymmetrical-dimethylhydrazine (UDMH) and monomethylhydrazine (MMH) in the cat (Goff et al., 1967; Sterman et al., 1972). It was subsequently established that a similar increase in the latency to MMH induced seizures and a reduced incidence of seizures could be obtained in behaving cats subjected to restraint in a nylon mesh bag (Bowersox et al., 1978). These and other reports in the seizure literature indicated that a suppression of movement could alter the toxic response to these propellants. However, one long-standing hypothesis concerning the generalized convulsions produced by hydrazine compounds relates to the formation of hydrazones with pyridoxal phosphate, a reaction which absorbs this coenzyme in the synthesis of glutamic acid decarboxylase (GAD) and gamma-aminobutyric acid (GABA), substances with synaptic inhibitory functions in the central nervous system (Clark et al., 1968; Wood and Peesker, 1974; Meldrum, 1975). Indeed, treatment with pyridoxine prevents hydrazine-induced seizures, presumably by restoring the synthesis of these inhibitory transmitter substances (Medina, 1963; Clark et al., 1968). We were interested, therefore, in examining the protection resulting from physical restraint within the context of these neurochemical dynamics.

The present study investigated the influence of immobilization on susceptibility to MMH convulsions in the rhesus monkey. Recent studies of this animal in our laboratory have focused both upon seizure response to MMH (Sterman et al., 1978) and EEG correlates of immobilization (Sterman et al., 1977; Holcombe, 1978), thus providing a background for the present investigation. Convulsive response and selected prodromal behaviors were compared in control and immobilized animals subjected to MMH intoxication and in animals protected from MMH convulsions with pyridoxine. It was necessary also to establish a dose-response function for the protective effects of pyridoxine in this animal.

METHODS

Nine adult, female rhesus monkeys (*Macaca mulatta*), within a normal weight range of 4 to 6 kg, participated in this study. All animals were adapted to a primate restraint chair for a period of six months. These chairs were modified by removal of the waist plate to allow the animal to rotate a full 360°. Food and fluid were provided daily and the monkeys were housed as a colony in an isolated room measuring 12 ft by 15 ft and maintained by the same caretaker on weekdays. The room lighting was controlled automatically and provided a 14:10 hour light-dark schedule.

Each animal was assigned randomly to one of three groups, with three animals per group. The first group (I) functioned as a control and underwent standard

testing for MMH seizure response. The standard testing procedure was similar to that developed in a previous study (Sterman et al., 1978). On the day preceding testing the animals were fed a light noon meal and then food was withheld until the test was completed. On the morning of the test day each animal was weighed in her restraining chair and isolated from the other animals by a sound attenuating partition. A large digital clock was placed on a table next to the animal. A video monitoring system placed in front of the animal was used to provide continuous observation and permanent recordings of behavioral responses to MMH. Each animal then received a 15 mg/kg injection of MMH, with the dose divided equally between the quadriceps muscles, bilaterally. All injections were administered between 9 and 11 AM. The drug was obtained from Matheson, Coleman and Bell, Norwood, Ohio (MW = 46.07 gm/mol, sp. gr. = 0.852) and was diluted to 20 mg/ml in normal saline. The test was terminated after a criterion 4 hr period, and a protective dose of pyridoxine hydrochloride and barbiturate was administered. If seizures developed during the 4 hr test period the trial was terminated with a therapeutic injection of pyridoxine and barbiturate after the third generalized seizure.

The second group (II) underwent the same testing procedure except that animals were placed in arm restraint 10 min after the administration of MMH. For this purpose, leather bracelets were placed at the elbow and wrist of each arm and attached to the frame of the restraining chair. For the third group (III) the standard testing procedure was modified by administering either 2.5, 5 or 10 mg/kg doses of pyridoxine hydrochloride, intramuscularly, 10 min after the injection of MMH, and repeated in counterbalanced order for each dose level.

The effect of these various treatments on convulsive response was evaluated in several ways. Previous studies with MMH have indicated that seizure susceptibility to this compound can be measured both by the latency to an initial generalized seizure and by the number of subsequent generalized seizures following exposure (Sterman et al., 1978). Latency to the initial generalized convulsion was measured here in minutes post-injection, by reference to the video recordings. A criterion limit of three generalized convulsions was established also in order to protect the animals from the possible development of respiratory failure with continuing seizures. Latencies to this criterion were measured as well and the trial terminated, as described above.

In addition to these measures of convulsive response certain specified behaviors were tabulated from the video recordings and compared among groups. These included minutes of sustained behavioral quiescence, minutes of sustained behavioral agitation, episodes of retching (emesis), and minutes containing pre-ictal events defined as (1) facial grimace with eye blinks, (2) head or limb jerks and/or (3) limb clonus. Statistical comparison of group characteristics was achieved using Analysis of Variance and multiple t-tests.

RESULTS

A comparison of convulsive responses and behavioral measures for the three groups studied is presented in Table 1. Both initial and final seizure latencies are shown, the test being terminated with protective medications after the third consecutive seizure. The mean latency to generalized convulsion for the untreated

TABLE 1

Comparison of convulsive latencies and incidence of pre-convulsive responses to 15 mg/kg dose of monomethylhydrazine in three groups of rhesus monkeys. (SQ = minutes of sustained quiescence; SA = minutes of sustained agitation; emesis = retching behavior; pre-ictal events = grimace with eye blinking, limb jerk, clonus.)

GROUP	SQ	SA	EMESIS	PRE-ICTAL EVENTS	LATENCY TO CONVULSION (MIN)	
					INITIAL	THIRD
I: Control						
1	21	2	22	14	65	95
2	18	14	11	13	74	100
3	25	1	16	12	69	92
$\bar{X}$	21.3	5.7	16.3	13.0	69.3	95.7
σ	±3.5	±7.2	±5.5	±1.0	±4.5	±4.0
II: Restraint						
1	12	19	0	0	none	-
2	21	3	0	0	none	-
3	39	11	0	0	none	-
$\bar{X}$	24.0	11.0	0	0	-	
σ	±13.7	±8.0	-	-		
III: Pyridoxine						
1	31	1	19	0	none	-
2	36	0	10	0	none	-
3	19	4	5	0	none	-
$\bar{X}$	28.7	1.7	11.3	0	-	
σ	±8.7	±2.1	±7.1	-		

control group was 69.33 ± 4.51 min. All of these animals exhibited generalized convulsions and all reached the criterion limit of three seizures within the first 100 min of observation, with a mean final latency of 95.67 ± 4.04 min. In contrast, none of the animals receiving doses of pyridoxine above 2.5 mg/kg (i.e., 5 and 10 mg/kg) exhibited generalized convulsions during the entire 240 min test period. Four animals were tested at the 2.5 mg/kg dose. Two showed no convulsive response while the other two showed somewhat delayed but complete generalized seizures. This dose, tested under these conditions, can be considered as a 50% protective level for MMH in the rhesus monkey. For this reason all subsequent comparisons were based on tests using the 10 mg/kg dose of pyridoxine.

Finally, none of the restraint group exhibited generalized convulsions during the entire 240 min test period. At the end of this period, however, one of the restraint group animals seized when approached for therapeutic drug administration.

Other behavioral measures were tabulated during the first 70 min post-MMH administration for all groups. This period approximated the mean initial seizure latency for control group animals, a limiting factor in this evaluation. Statistical analysis indicated that significant group differences were limited to the incidence of emesis and pre-ictal events, only. The restraint group animals showed no emesis during this period of tabulation. Moreover, no evidence of pre-ictal events was noted in the video records for either the restraint or pyridoxine group (10 mg/kg) during this initial 70 min period. Tabulation of these behavioral measures was extended across the 240 min test period for restraint and pyridoxine groups and the count divided into successive 85 min periods following the initial evaluation. The results of this assessment are shown in Table 2. It can be seen that animals in both groups eventually displayed retching and pre-ictal behaviors. Emesis was significantly delayed in the restraint group, becoming more frequent with time. The opposite pattern was noted in the pyridoxine group. Pre-ictal events were delayed in both groups but were more frequent by the middle of the test period in restrained animals. These responses were comparable in the two groups during the last period of observation.

While overall activity levels were statistically comparable in all groups, the patterns of activity observed were different. Control animals usually became quiet within a brief period following MMH administration. This quiescence was disturbed periodically by overt emesis. A period of behavioral agitation, sometimes with emesis, also immediately preceded generalized convulsions. Pyridoxine treated animals showed a similar behavioral pattern but with reduced agitation, even in association with emesis. In contrast, the restrained animals were characterized behaviorally by alternating periods of struggling against their encumbrance followed by sustained, motionless quiescence often with unusual head positioning, the latter constituting an "immobilization response" described previously (Holcombe et al., 1978). The net effect of these differing behavioral patterns was an overall quantitative parity between groups in terms of quiescence, a tendency towards reduced agitation following pyridoxine and a tendency towards increased agitation among restrained animals. However, these differences were not statistically significant.

TABLE 2

Mean incidence of emesis and pre-ictal events in restraint and pyridoxine monkey groups during three successive periods of observation following 15 mg/kg MMH.

OBSERVATION PERIOD	EMESIS		PRE-ICTAL EVENTS	
(MIN POST MMH)	Restraint	Pyridoxine	Restraint	Pyridoxine
0-70	0	11.3	0	0
71-155	2.0	6.3	8.0	1.3
156-240	4.0	1.0	8.3	7.6

DISCUSSION

The present findings indicate that under normal conditions a dose of 15 mg/kg of MMH is 100% convulsive for the chaired rhesus monkey. This conclusion is in agreement with similar findings from a previous study (Sterman et al., 1978). The mean initial seizure latency of 69.33 ± 4.51 min determined here was consistent with the latency value of 85.0 ± 19.58 reported earlier. The present study also showed that MMH convulsions were prevented by pyridoxine, thus confirming the protective effects of this coenzyme for GAD in relation to hydrazine toxicity. This finding was refined further by establishing a 50% protective dose level in the monkey at 2.5 mg/kg. Finally, the evidence presented here once again indicated that restraint can attenuate toxic responses to these compounds as well. This finding also is in agreement with an earlier study by Bowersox et al. (1978) which reported a similar attenuation of MMH seizures in cats restrained in a nylon mesh bag.

As mentioned previously, it has been suggested that the seizures produced by MMH result ultimately from disruption of the synthesis of GAD and GABA, substances with established pre- and post-synaptic inhibitory functions in the central nervous system (Curtis and Watkins, 1960; Willot, 1974; Meldrum, 1975). While the protective effect of pyridoxine can be understood within this context, it is more difficult to comprehend the mechanism by which physical restraint can influence these neurochemical dynamics. Moreover, it is clear that restraint can influence other types of seizures as well. Thus, audiogenic seizures were attenuated in physically restrained rats (Lindsley et al., 1942; Griffiths, 1953) and mice (Willot, 1974), and seizure suppression was noted in the photosensitive baboon (*Papio papio*) by Ehlers and Killam during restraint and by Naquet and associates after neuromuscular paralysis (personal communications).

How might the anticonvulsant effects of restraint be mediated? It could be suggested that arousal or attention factors associated with restraint serve to activate the central nervous system and, as is sometimes observed with convulsive disorders, prevent or abort the occurrence of seizures. There are numerous problems with this conclusion. First, the restrained animal shows recurrent

periods of immobility and synchronous EEG patterns that are not consistent with a high level of arousal (see below). Furthermore, behavioral and EEG patterns preceding seizures with MMH and other hydrazines are themselves indicative of very high arousal (Sterman et al., 1969a; Schlesinger and Uphouse, 1972). Finally, any sensory stimulation delivered during the vulnerable period with these drugs will actually elicit convulsions (Sterman et al., 1969), as was the case with one of the restraint animals in this series. These various considerations appear to rule out CNS activation as an explanation for the protective effect observed here with restraint.

Experiments examining changes in somatosensory evoked potentials following MMH exposure disclosed a relatively specific facilitation of the primary negative potential preceding the onset of generalized seizures, and indicated that both evoked potential changes and seizures were significantly delayed by either neuromuscular paralysis (Goff et al., 1967, 1970; Sterman et al., 1972) or learned suppression of movements (Sterman et al., 1975; Sterman, 1976). It was suggested that hydrazine compounds cause evoked potential facilitation by blocking normal inhibitory post-synaptic potentials. This interpretation is consistent with the neurochemical findings of disrupted GAD and GABA synthesis following convulsive doses of hydrazines. Thus, it could be proposed that restraint or paralysis delays the depletion of inhibitory transmitter reserves by reducing somatosensory afferent bombardment of the central nervous system. However, to the extent that somatosensory afferent activity is related to movement, the present findings would be unsupportive of this idea since overall somatic activity was, if anything, greater in restrained animals.

In a previous study of arm restraint in the chaired rhesus monkey we described a specific behavioral state which was termed the "immobilization response." During this state the animals became motionless and simultaneously recorded EEG patterns over rolandic cortex disclosed a localized increase in rhythmic activity centered at 12-15 c/sec. Power-spectral analysis indicated that this EEG pattern was strictly associated with immobilization and was sustained even when the animal was aroused with sensory stimuli, despite the fact that lower frequencies were attenuated. Similar EEG changes were reported in the chair-restrained baboon (*Papio papio*) when the head was fixed in a special headholding device (Bouyer et al., 1978). We were particularly interested in this behavioral and EEG response to immobilization because other studies had shown that the learned enhancement to rhythmic central cortical 12-15 c/sec activity, achieved with EEG operant conditioning, was associated with motionlessness and protected both cats and monkeys from seizures induced by MMH (Sterman, 1976; Sterman et al., 1978). Since in the cat this EEG pattern was correlated with a suppression of movement (Wyrwicka and Sterman, 1968; Sterman et al., 1969b; Rougeul et al., 1972), a reduction in tonic motor discharge (Chase and Harper, 1971), and an attenuation of motor reflex activity (Babb and Chase, 1974), it was suggested that protection resulted from an active facilitation of motor inhibition. Somatosensory evoked potential studies in the cat indicated also that thalamic conduction of somesthetic signals was specifically attenuated during the learned production of this EEG rhythm (Howe and Sterman, 1973), suggesting a concurrent attenuation of somatosensory activation of cortex. Both behavioral and EEG patterns during arm restraint in the rhesus monkey are similar to those observed during operant conditioning of rolandic 12-15 c/sec EEG patterns. It is possible, therefore, that a state of increased motor inhibition and attenuated sensory response also

accompanies the recurrent periods of immobilization during arm restraint. This *state*, and not the behavior alone, may indeed be anticonvulsant. A condition of attenuated somatosensory response might also account for the reduced emesis observed in restrained animals after MMH intoxication. It seems clear that specific neurochemical responses elicited by sustained motionlessness can influence the toxic response to MMH.

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